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Determinants of Positive Histologic Margins and Residual Tumor After Lumpectomy for Early Breast Cancer: A Prospective Study With Special Reference to Touch Preparation Cytology

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Background and Objectives: Removal of the entire tumor by breast-conserving surgery is important, but the determinants of adequate excision have not been established.
Methods: A prospective study of 55 consecutive lumpectomies for early breast cancer was performed to study the correlation between touch preparation cytology and histologic margins and the determinants of positive histologic margins and residual disease after the initial excision.
Results: The correlation between touch preparation cytology and histologic margins was poor: sensitivity and specificity were 37.5% and 85.1%, respectively. The histologic margins were positive in 8 cases (14.5%) and were related to the presence of intraductal carcinoma and to the large pathologic size of the index tumor. Re-excision specimen of the tumor bed (34 of 55 cases) contained residual cancer in seven cases (20.6%). Multifocal and nonpalpable index tumors predicted residual cancer. Residual disease was found in 37.5% of the cases (3 of 8) with positive and in 15.4% of the cases (4 of 26) with negative histologic margins.
Conclusions: Touch preparation cytology cannot be recommended as a method of assessing lumpectomy margins for early breast cancer. Histologic margins are misleading in predicting residual cancer in re-excision specimens. To minimize the risk of residual cancer, wide excision or mastectomy should be considered in the management of multifocal and nonpalpable tumors. *J. Surg. Oncol. 1997;66:248–253.*

KEY WORDS: **breast neoplasm; breast-conserving surgery; cancerous residua; re-excision**

INTRODUCTION

The residual microscopic carcinoma after breast-conserving surgery may account for the increased risk of local recurrence [1–5]. Thus, there is a growing desire to ensure the removal of all tumor tissue at lumpectomy. When the first attempt fails to provide histologically tumor-free margins, re-excision may be necessary. The reported proportions of residual carcinoma in re-excision specimens have varied according to the extent of the primary biopsy procedure from 11 to 100% [1,2,4,6–10]. The standard histologic examination of biopsy specimens has important limitations, because only a very small proportion of the specimen's outer surface can be analyzed [5]. In 1991 Cox et al. [11] reported a new intraoperative

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method, touch preparation cytology, for evaluating microscopic disease in the entire resected breast lumpectomy surface. The aim of the prospective study was to compare touch preparation cytology with standard histologic examination of the lumpectomy margins and to study the determinants of positive histologic margins and residual cancer in re-excisions.

MATERIALS AND METHODS

From October 1994 until November 1995, 53 consecutive patients who underwent 55 lumpectomies for early breast cancer in the Oulu University Hospital were prospectively evaluated to compare the cytologic and histologic specimen margins. Two lumpectomies were re-excisions. Thirty-six of the 55 lumpectomies (65.5%) were performed by wire guidance and radiographic control.

The following parameters were recorded: age, preoperative palpatory and mammographic findings, size of the biopsy specimen (largest dimension accurately measured in 51 of 55 specimens), pathology of index tumor (size, stage, presence vs. absence and extent of noninvasive cancers and possible multifocality). Microscopic foci of cancer encountered within or close to the same quadrant as the index cancer were regarded as signs of multifocality and those seen in quadrants remote from the index cancer as signs of multicentricity.

In lumpectomy, the surgeon removed the tumor with a rim of grossly normal tissue, usually 1–2 cm or more. During surgery, cellular samples were obtained for touch preparation cytology as described by Cox et al. [11]. Two to six slides were used, depending on the specimen size. An additional slide of the tumor itself as a positive cytologic control was taken from 12 of the 55 tumors. After that, the specimen was inked for permanent histologic examination. The touch preparation cytology slides were categorized after examination as positive if malignant cells were present, negative if malignant cells were not seen, and inconclusive when the cellular material on the slide was inadequate to allow conclusions. A microscopic margin was considered to be positive if the tumor was present within the inked surface, and otherwise it was considered negative. An extensive intraductal component (EIC) was considered to be present when in-situ cancer occupied 25% or more of the area encompassed by the infiltrating tumor or was widely present in random sections of grossly unremarkable breast tissue, or clearly extended beyond the infiltrating edge of the tumor into the surrounding breast tissue.

The mean age of the patients was 56 years (range 40–82 years). Thirty of the 55 tumors (54.5%) were nonpalpable. At preoperative mammography, 12 of the 55 tumors (21.8%) showed microcalcifications, 33 (60.0%) showed a mass and 8 (14.5%) a mass with microcalcifications. Two tumors (3.6%) were mammographically negative. The average breast tissue removed (largest dimension) at the baseline was 7.0 ± 2.3 cm (mean ± SD). The distribution of histologic types of breast carcinoma is shown in Table I. Twenty-three of the 55 specimens (41.8%) contained pure invasive and 10 pure noninvasive (in situ) tumor, while the remaining 22 cases contained both invasive and noninvasive tumor. In seven of these 22 cases the noninvasive tumor component was considered extensive (EIC). The mean pathologic size of the tumors (invasive + noninvasive component) was 1.8 ± 1.4 cm. According to the UICC [12], the pathologic stages 0, I and II accounted for 10 (18.2%), 30 (54.5%) and 15 cases (27.3%), respectively. Seven of the 55 tumors (12.7%) were multifocal.

TABLE I. Distribution of Histologic Types of Breast Carcinomas in 55 Lumpectomy Specimens

Histology	N
Invasive	
Ductal	31 (12)
Lobular	5 (4)
Tubular	5 (5)
Mucoid	2 (1)
Papillary	1
Metaplastic	1
Noninvasive	
Ductal	6 (4)
Lobular	4 (4)
Total	55 (30)

The figures in parentheses indicate the number of nonpalpable tumors.

Re-excision of the primary tumor bed was performed in 34 of the 55 cases (61.8%) because of uncertainty as to the adequacy of the surgical margins (5 mm or less) in the initial procedure. The same parameters were compared in the cases with and without residual cancer in the re-excision specimen. Chi-square analysis with Yates correction was used for a statistical comparison of categorical data. The Student's *t*-test was applied for continuous variable comparisons. Differences at or below the level of $P = 0.05$ were regarded as statistically significant.

RESULTS

Correlation of the Cytologic and Histologic Margins

The histologic examination of the specimens revealed positive margins in eight (14.5%) and negative margins in 47 (85.5%) of the 55 specimens. The correlation between histologic and touch preparation cytologic resection margins is summarized in Table II. The sensitivity, specificity, positive and negative predictive value and overall diagnostic accuracy of touch preparation cytology were 37.5%, 85.1%, 37.5%, 88.9% and 78.2%, respectively. The two inconclusive specimens were included in these calculations (Table II).

TABLE II. Correlation Between Histologic and Touch Preparation Cytologic Resection Margins in 55 Specimens

	Histologic margins		
Cytologic margins	Positive	Negative	Total
Positive	3	5	8
Negative	5	40	45
Inconclusive	0	2	2
Total	8	47	55

TABLE III. Presence of Ductal Carcinoma In Situ (With or Without Invasive Component) in Eight Tumors With Positive and 47 Tumors With Negative Histologic Margins After Lumpectomy

	Margin positive	Margin negative
DCIS	7	18
No DCIS	1	29
Total	8	47

DCIS, ductal carcinoma in situ.

Determinants of Positive Histologic Margins

A statistically significant correlation was found between positive histologic margins and the presence of ductal cancer in situ (with or without an invasive component) ($P = 0.028$) (Table III) but not with the presence of EIC. EIC was present in two of five margin-positive and in five of 40 margin-negative invasive tumors ($P = 0.35$). The mean pathologic size (invasive + noninvasive component) of the margin-positive index tumors (2.8 ± 1.7 cm) was clearly larger than the size of the margin-negative tumors (1.7 ± 1.3 cm) ($P = 0.023$). Notably, the specimen sizes (largest diameter) in both groups were almost identical (7.0 ± 1.6 cm vs. 7.0 ± 2.4 cm). No other parameters revealed any statistically significant difference between these groups.

Determinants of Residual Disease

A histologic examination of the 34 re-excision specimens (breast-conserving surgery 18, mastectomy 16) revealed residual disease at or near the primary resection margin in seven specimens (20.6%) and no residual carcinoma in 27 specimens (79.4%). The re-resection specimens contained two invasive cancers (tubular and mucoid), both with ductal carcinoma in situ, and five noninvasive cancers (three ductal cancers in situ and two lobular cancers in situ).

There was no significant difference in the histologic or cytologic margin status between the cases with or without residual cancer ($P = 0.39$ and $P = 0.80$, respectively) (Table IV). The re-excision specimens contained residual carcinoma in 37.5% (3 of 8) and 33.3% (2 of 6) of the specimens with histologically and cytologically positive margins, respectively. For negative margins, the corresponding figures were 15.4% (4 of 26) and 18.5% (5 of 27), respectively. Considering all the patients in which either histologic or cytologic margins were positive, only 30.8% (4 of 13) of the re-excisions revealed residual disease. One patient with residual disease had both histologic and cytologic margins positive.

Table V summarizes the significant differences in the seven index tumors that left residual cancer in the tumor-bed compared to the 27 tumors without residual disease. The differences in the distribution of other factors were statistically insignificant. EIC was present in two of the three residual-positive and in five of 22 residual-negative invasive tumors ($P = 0.37$). The average amount of breast tissue removed at lumpectomy was 6.2 ± 2.3 cm in seven cases with residual disease and 7.0 ± 2.2 cm in 27 cases without residual diseases ($P = 0.40$).

TABLE IV. Comparison of Histologic and Cytologic Margins to Residual Cancer Found in Re-Excision Specimens

	Residual cancer	No residual cancer	Total
Histologic margins			
Positive	3	5	8
Negative	4	22	26
Total	7	27	34
Cytologic margins			
Positive	2	4	6
Negative	5	22	27
Inconclusive	0	1	1
Total	7	27	34

TABLE V. Main Differences Between Seven Tumors With and 27 Tumors Without Residual Cancer in Re-Excision Specimens

	Residual cancer	No residual cancer	
Multifocal	4 (4)	1 (1)	$P = 0.003$
Unifocal	3 (3)	26 (12)	
Palpable	0	14	$P = 0.040$
Nonpalpable	7	13	
Mammography			$P = 0.073$
MC[a]	5 (5)	6 (6)	
Mass or density	1 (1)	16 (6)	
MC + density	1 (1)	3	
Normal	0	2 (1)[b]	

The figures in parentheses indicate nonpalpable tumors.
[a]Microcalcifications.
[b]Detected at ultrasonography.

DISCUSSION

Numerous reports have been published on the importance of adequate tumor-free margins in lumpectomy specimens [1,2,4,6,10,13–24]. Most of these reports have

investigated the correlation between surgical margins and local recurrence [10,13–22] and some of the occurrence of post-biopsy residual cancer [2,4,6,10]. Only a few reports have focused on factors predicting the adequacy of margins after initial biopsy [23,24]. These reports have shown the difficulties encountered in assessing margins by a standard histologic examination. It has been calculated that complete display of the surface of a 2-cm spherical carcinoma would require more than 3,000 histologic sections. Therefore, alternative methods have been suggested [1,5,11]. Cox et al. [11] introduced in 1991 touch preparation cytology for evaluating microscopic disease in breast lumpectomy margins. Theoretically, the cytologic examination evaluates the entire resected surface, and it would therefore be logical to assume a higher likelihood of discovering at least all cases with positive histologic margins and even some additional cases missed by histologic examination. Compared to permanent histologic sections, the sensitivity, specificity and overall diagnostic accuracy reported by Cox et al. were 100%, 96.6% and 97.3% respectively. However, the corresponding figures in the present study (37.5%, 85.1% and 78.2%) were clearly lower. Touch preparation cytology missed five of eight histologically positive margins. The reasons for the inferior results in our study are not obvious. One reason may be that we did not systematically use an additional cytologic slide of the tumor itself as a positive control and that we are less experienced in interpreting touch preparation cytologic slides than Cox et al. Unlike them, we also included the inconclusive specimens in our analysis in order to avoid falsely high accuracy figures [25].

In this study, 14.5% of the cases showed positive histologic margins, while the rates previously reported in the literature vary from 12 to 30%. The only significant factors predicting positive histologic margins were large pathologic tumor size and the presence of ductal carcinoma in situ. One previous study noted a correlation between tumor size and margin involvement [23], but no such correlation was found in another study [24]. In the latter series, EIC was significantly associated with positive margins. Neither of the these retrospective series had specified specimen size, which makes a comparison of the results difficult. In the present study, the specimen sizes in the margin-positive and margin-negative groups were quite equal. Since the tumors with positive margins were larger than the ones with negative margins, the sizes of the former must have been underestimated either clinically or mammographically. All but one of the margin-positive cancers were at least partially noninvasive. As intraductal cancer usually does not induce the kind of desmoplastic reaction typical of invasive cancers, it cannot be palpated as different from the normal surrounding breast tissue during surgery. Often, the only manifestation of intraductal carcinoma is a cluster of microcalcifications at mammography. It is essentially important to carefully assess the size and distribution of the calcifications on preoperative mammograms and specimen radiographs in order to avoid insufficient removal of the tumor. It is known, however, that not all intraductal tumors are seen at mammography and that tumor-free margin at specimen radiography is not a good predictor of histologically uninvolved margins [26].

Only 20.6% (seven of 34) of the re-excision specimens in our study contained residual carcinoma. In previous reports, this proportion has varied from 11% to 100%, depending on the extent of the primary excision [1,2,4,6–10,27]. Notably, the histologic or cytologic margin status was not related to residual cancer in re-excision specimens. Frazier et al. [4] also pointed out that the assessment of microscopic margins may be misleading, since 47.5% of the patients with involved margins had no residual tumor, and 29.8% of those with clear or close margins subsequently had residual tumor upon re-excision. This is probably one of the reasons for the conflicting reports concerning the prognostic importance of surgical margins for local control after breast-conserving surgery [10,13–22,28]. One reason for negative residual cancer after positive lumpectomy margins may be that the amount of residual cancer is too small to be detected by a standard histologic examination. Multifocality, on the other hand, explains the residual cancers found after negative lumpectomy margins. According to Holland et al. [29], tumor resection with 3 to 4 cm margins would have left invasive or noninvasive residual cancer in the remaining breast tissue in 4 to 9% of cases. According to Morimoto et al. [30], lumpectomies removing a T1-tumor with a margin of 2 cm would leave residual cancer foci in the breast in about 20% of cases. The proportion of residual cancer in the re-excision specimens of our series was 20.6% and multifocality was the most important predicting factor.

Another predictor of residual disease was nonpalpability of the index tumor. The most probable reason for this is that nonpalpable cancers were more often multifocal and noninvasive than palpable ones. Nonpalpable breast tumors have also been reported to have a higher rate of postbiopsy residual disease [31]. Moreover, microcalcifications in preoperative mammograms predicted residual disease. This was not unexpected, as microcalcifications are an important sign of intraductal carcinoma, and their size on mammograms is known to underestimate the size of the carcinoma [32]. All residual tumors contained noninvasive cancer.

The presence of EIC in palpable cancers increased the incidence of residual carcinoma in re-excision specimens from 48% to 88% in one retrospective study [2]. In our study, EIC was not found to be related to residual cancer. This result cannot, however, be considered reliable because of the small number of invasive cancers with re-

sidual disease. EIC has also been considered prognostic for local failure after breast-conserving surgery, but the results are controversial [1,3,10,13,16,18–22,33]. Our results suggest that, instead of being related to EIC itself, the associated characteristics are related to the local failure.

CONCLUSIONS

Pathologically large tumors containing intraductal cancer (with or without an invasive component) are prone to have histologically tumor-positive margins in lumpectomy specimens. Touch preparation cytology cannot be recommended for routine assessment of lumpectomy margins because of its poor correlation with histologic margins. On the other hand, the histologic assessment of margins is misleading in predicting residual cancer in re-excision specimens. Only multifocality and nonpalpability of the index tumor predict histologically detectable residual disease. To minimize the risk of residual cancer in these tumors, wide excision or mastectomy should be considered.

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